

Protein Repeats from First Principles

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Abstract

Some natural proteins display recurrent structural patterns. Despite being highly similar at the tertiary structure level, repetitions within a single repeat protein can be extremely variable at the sequence level. We propose a mathematical definition of a repeat and investigate the occurrences of these in different protein families. We found that long stretches of perfect repetitions are infrequent in individual natural proteins, even for those which are known to fold into structures of recurrent structural motifs. We found that natural repeat proteins are indeed repetitive in their families, exhibiting abundant stretches of 6 amino acids or longer that are perfect repetitions in the reference family. We provide a systematic quantification for this repetitiveness. We show that this form of repetitiveness is not exclusive of repeat proteins, but also occurs in globular domains. A by-product of this work is a fast classifier of proteins into families, which yields likelihood value about a given protein belonging to a given family.

Introduction

Natural repeat proteins are coded with tandem copies of similar amino acid stretches. These molecules are broadly classified according to the length of the minimal repeating unit [1]. Short repetitions of up to five residues usually form fibrillar structures, while repetitions longer than about 60 residues frequently fold as independent globular domains. There is a class of repetitive proteins that lays in between these for which folding of the repeating units is coupled and domains are not obvious to define [2,3]. Despite being highly similar at the tertiary structure level, repeats within a single protein or in different members of

a protein family can be extremely variable at the sequence level [4], complicating the detection and classification of repeats [1].

There are many methods to identify repeats in sequences. Some are based on the self-alignment of the primary structure [5] and others implement spectral analysis of pseudo-chemical characteristics of the amino acids [6]. Since the same structural motif can be encoded by sequences that seem completely unrelated, it is not surprising that alignment-based methods fail to infer true structural repeats. The solutions to find inexact repeats in sequences [7, 8] include alphabet replacements using scoring matrices, sophisticated notions of sequence similarity based on an allowed percentage of mismatches, and elaborated mathematical representations such as Hidden Markov Models. To a very large extent these solutions have been satisfactory. However, these methods rely on the fine-tuning of different parameters in order to account for the inexactness of repeats (thresholds for alphabet scoring matrices, allowed percentage of mismatches, e-values for Hidden Markov Models and others). The definition of what constitutes or not a hit for the model remains subject to some threshold definition.

In this work we turned to “first principles”, starting with a mathematical definition of biological repeats and we developed a repeat finding method with no adjustable parameters. We use the concept of maximality and maximal repetition (MR). In the context of a protein sequence, a MR is a block of amino acids that occurs two or more times and any of its extensions occurs fewer times. In case a long block in a protein sequence is equal to another, except for one letter, then there will be two repetitions, one to the left and one to the right of that single letter. It is well known that long stretches of perfect repeats are infrequent in natural proteins, even in those that fold into structures of recurrent structural motifs. However, we observe that a large portion of a protein sequence can be described by short stretches of amino acids that occur in other members of a protein family. Thus, a protein family operates as a catalogue of all the possible variations that a block can adopt in any of its members. We quantify the repetitions we measure how well a given sequence is covered by the repetitions occurring in its family. The method is implemented efficiently by an algorithm with a $O(n \log n)$ computational complexity, where n is the size of the protein sequence being tested. From this quantification we directly obtain a way to decide if one family is more repetitive than another. In addition, this quantification allows us to derive a measure of likelihood for a given sequence to belong to a given family.

Notation and preliminary definitions

Let \mathcal{A} be an alphabet, which is a finite set of symbols. We consider sequences of symbols in \mathcal{A} . The length of a sequence s is denoted by $|s|$. We address the positions of a sequence s by counting from 1 to $|s|$. With $s[i..j]$ we denote the sequence that starts in position i and ends in position j in s . If i or j are out of range then $s[i..j]$ is equal to the empty sequence. We say u occurs in s if $u = s[i..j]$ for some i, j . In case s starts with u we say that s is an extension of

u .

Definition 1 (Gusfield [8]) A maximal repeat (MR) is a sequence that occurs more than once in w , and each of its extensions occurs fewer times. We write $\mathcal{M}(s, n)$ to denote the set of MRs of lengths greater than or equal to n , that occur in the sequence s .

The set of MRs of $s_1 = abcdeabdcdfbcdebcd$ is $\{abcd, bcde, bcd\}$. Observe that $abcd$ and $bcde$ are the longest MRs, occurring twice. But bcd is also a MR because it occurs four times in s_1 , and every extension of bcd occurs fewer times. On the contrary, bc is not a MR because both bc and bcd occur four times, contradicting the condition that the extension must occur fewer times (see Fig. 1A). The set of MRs of $s_2 = aaaa$ is $\{aaa, aa, a\}$ where aaa is a MR occurring twice, aa occurs three times and a four times. The set of MRs of $s_3 = ab$ is empty.

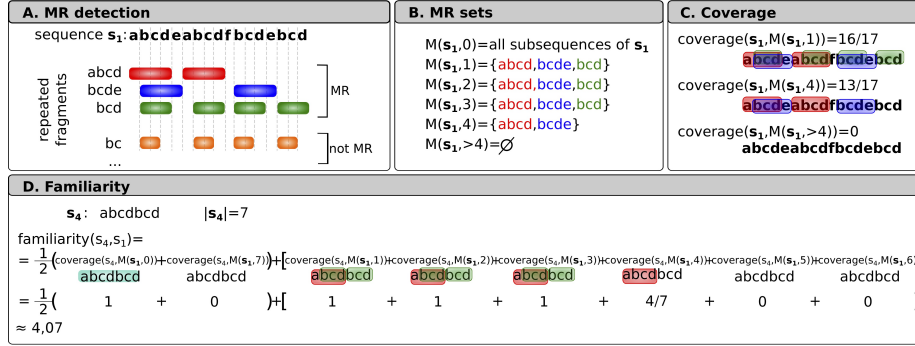


Figure 1: **Scheme of the procedure to obtain *familiarity* function value.**

A) Maximal repeats (MR) are computed for input sequence. B) MR sets are filtered by the minimum MR length. C) MR sets are overlapped to input sequence and coverage is calculated. D) *familiarity* is computed based on coverage at every length.

From the given examples is easy to see that MR occurrences can be nested and overlapping. The MRs in any given sequence s can have lengths between 1 and a maximum of $|s|-1$ (this maximum is reached only when the sequence is a chain of the same letter, as $aaaa$). The total number of different MR patterns in a sequence of length $|s|$ is at most $|s|$ because there is at most one different MR starting at each position.

Definition 2 Let S be a set of n sequences over the alphabet \mathcal{A} , $S = \{s_1, s_2, \dots, s_n\}$. The set of MRs in S is the set of MRs of the sequence obtained by concatenation of all sequences in S , interleaved with pairwise different symbols $\$1, \dots, \$n-1$ that are not in \mathcal{A} . Thus, the set of MRs in S is the set of MRs in $s_1 \$1 s_2 \$2 \dots \$n-1 s_n$.

Since each $\$i$, for $i = 1, 2, \dots, n-1$, occurs only once in the concatenated sequence there will be no MRs containing them. Since the symbols $\$i$, for

$i = 1, 2, \dots, n-1$, are pairwise different, the set of MRs is invariant respect to the order in which we concatenate the sequences s_1, s_2, \dots, s_n . Concatenation of any permutation of the sequences s_1, \dots, s_n produces the same set of MRs.

Observe that finding the set of MRs in a set of sequences requires more than treating them individually. If s and t are two sequences and $\$$ is a symbol not occurring in s nor in t , the MRs in $w = s\$t$ may be different from getting the individual MRs and take their union, because a repeat in w may occur only once in s and only once in t .

The familiarity function We define the familiarity function that measures how much of a given protein sequence is covered by MRs from certain family. The greater the familiarity value, the most likely the protein sequence to belong to the family. We first introduce the classical notion of *coverage* of a sequence by a set of MRs, which measures the number of positions in the sequence that are covered by the MRs in the set. We write \mathcal{A}^* for the set of all sequences over \mathcal{A} , and $\mathcal{P}(\mathcal{A}^*)$ the set of all the parts \mathcal{A}^* , which represents the collection of all the different sets of sequences over \mathcal{A} . As usual, we write \mathbb{N} and \mathbb{Q} for the set of natural and rational numbers, respectively.

Definition 3 *The function $\text{coverage} : \mathcal{A}^* \times \mathcal{P}(\mathcal{A}^*) \rightarrow \mathbb{Q}$ is such that for any sequence s and any set of sequences R*

$$\text{coverage}(s, R) = \frac{\#\{j : \exists i \in \mathbb{N}, \exists r \in R, s[i..i + |r| - 1] = r\}}{|s|}. \quad (1)$$

Thus, $\text{coverage}(s, R)$ is a rational number between 0 and 1.

For example, for $s_1 = abcdeabdcdfbcdebcd$ and $R = \mathcal{M}(s_1, 1) = \{abcd, bcde, bcd\}$ we have $\text{coverage}(s_1, R) = 16/17 \approx 0.94$ (see Fig. 1C).

The *familiarity* function measures how much of a sequence is covered by a set of MRs that occur in a family.

Definition 4 *The familiarity function $: \mathcal{A}^* \times \mathcal{A}^* \rightarrow \mathbb{Q}$ is defined as follows. For any sequence s and any sequence t ,*

$$\text{familiarity}(s, t) = \frac{\text{coverage}(s, \mathcal{M}(t, 0)) + \text{coverage}(s, \mathcal{M}(t, |s|))}{2} + \sum_{i=1}^{|s|-1} \text{coverage}(s, \mathcal{M}(t, i)) \quad (2)$$

Note that $\text{familiarity}(s, t)$ uses $\mathcal{M}(t, 0)$ which, by definition, gives all the blocks of the sequence t . Thus, for every sequence s and t the function $\text{familiarity}(s, t)$ is a number between 0 and $|s|$. For example, the $\text{familiarity}(s_4, s_1)$ of $s_4 = abcdabcd$ and $s_1 = abcdeabdcdfbcdebcd$ is around 4.07 because the set of MRs of s_1 is $\{abcd, bcde, bcd\}$, and then $\text{familiarity}(s_4, s_1) = \frac{1+0}{2} + 1 + 1 + 1 + \frac{4}{7} + 0 + 0 \approx 4.07$ (see Fig. 1D).

If the *familiarity* function is evaluated with the same sequence in the two arguments, *familiarity*(*s*, *s*) the result tells how much of the sequence *s* is covered by its own MRs. For example, the *familiarity*(*s*₅, *s*₅) of *s*₅ = *abcabca* is 4.5 because the set of MRs of *s*₅ is {*a*, *abca*}, and then *familiarity*(*s*₅, *s*₅) = $\frac{1+0}{2} + 1 + 1 + 1 + 1 + 0 + 0 = 4.5$. In the case of *s*₆ = *aaaaaaa* the *familiarity*(*s*₆, *s*₆) is 6.5 because the set of MRs of *s*₆ is {*a*, *aa*, *aaa*, *aaaa*, *aaaaa*, *aaaaaa*}, and then *familiarity*(*s*₆, *s*₆) = $\frac{1+0}{2} + 1 + 1 + 1 + 1 + 1 + 1 = 6.5$. In these examples, *s*₆ reaches a higher coverage than *s*₅ when using MRs internal to each of them.

For a given set of sequences, let *t* be the concatenation of its elements separated by pairwise different symbols. Then, *familiarity*(*s*, *t*) indicates how much of the sequence *s* coincides with the MRs in *t*. For example, the *familiarity*(*s*₅, *t*₁) of *s*₅ = *abcabca* and *t*₁ = *aa\$₁ab\$₂adddd\$₃bca* is around 1.21 because the set of MRs of *t*₁ is {*a*, *b*, *d*, *dd*, *ddd*}, and then *familiarity*(*s*₅, *t*₁) = $\frac{1+0}{2} + \frac{5}{7} + 0 + 0 + 0 + 0 + 0 \approx 1.21$. Hereafter we will just use the name of a family in the second argument of the *familiarity* function, to denote the concatenation of all the sequences present in that family, separated by pairwise different symbols.

Results and Discussion

Maximal repeats inside protein sequences

Since some proteins contain clear repetitive motifs in structure, we wondered how much of that repetitiveness is maintained at the sequence level. We analyzed the occurrence of exact repetitions on members of the Ankyrin repeat protein family (ANK_{*t*}), for which many structures have been solved. Ankyrins constitute the most abundant class of natural repeat proteins, and have been extensively studied. We computed the maximal repeats (MRs) inside each protein, for all possible lengths (from a minimum length of 1 to the maximum possible, the length of the sequence minus 1). Fig. 2 shows the coverage given by MRs inside *s* = *IκBα* (Uniprot ID: *P25963*), a member of the ANK_{*t*}, for different minimum MRs lengths ($\mathcal{M}(\text{I}\kappa\text{B}\alpha, i)$ for $i = 1, \dots, 6$). We find that this protein has 102 MRs distributed as follows: 20 MRs of length 1, 65 MRs of length 2, 11 MRs of length 3, 3 MRs of length 4, 2 MRs of length 5 and only one MR of length 6. The detected MRs are not evenly distributed along the sequence but clustered at specific positions. In most cases the shorter MRs are nested within longer MRs. Moreover, several MRs occur in the same parts of the sequence. These are overlapping occurrences of MRs.

We analyzed the coverage of the primary structure of the protein IκBα using sets of MRs of increasing minimum length (Fig. 3, black dots). Trivially, the coverage is maximum when MRs of length 1 are considered, because in general every amino acid occurs at least twice inside the protein and then, every position in the protein is covered by some MR of length 1. The coverage is reduced as the minimum MR length is increased, reaching 0 for the values of $i = 7, \dots, |s|$, as there are no exact repetitions larger or equal than 7 residues. Coverage values for all the members of the ANK_{*t*} were calculated for maximal lengths

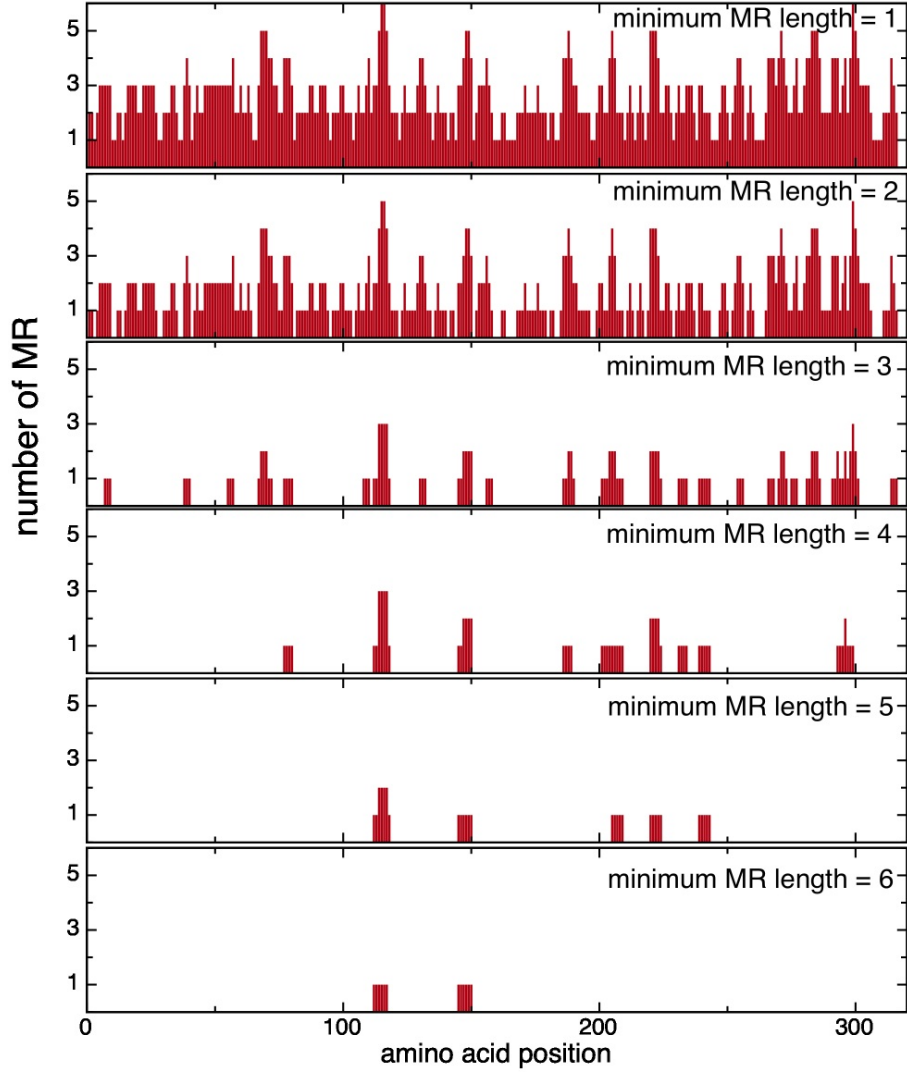


Figure 2: **Number of maximal repeats (MR) that affect each position on a trial sequence.** The $I\kappa B\alpha$ protein sequence was used as input, the MR set were computed by $\mathcal{M}(I\kappa B\alpha, i)$ with $i = 1 \dots 6$. The panels show the counts per position for the different MR sets sorted by minimum length.

$i = 0, \dots, 10$ (see Table in Table S1). For each ANK_t protein, the set $M(s, 1)$ produces almost full coverage (the coverage function is $\simeq 1$). However, the set of MRs of length i decays rapidly as i increases, and very soon the set of MRs becomes empty. The set of MRs of lengths $i \geq 6$ contrasts with the MRs that can be found in structures, where no sequence information is taken into

account [3]. In general, most of the Ankyrin repeat proteins (ANKs) analyzed in this work, are almost entirely covered by structural repeats.

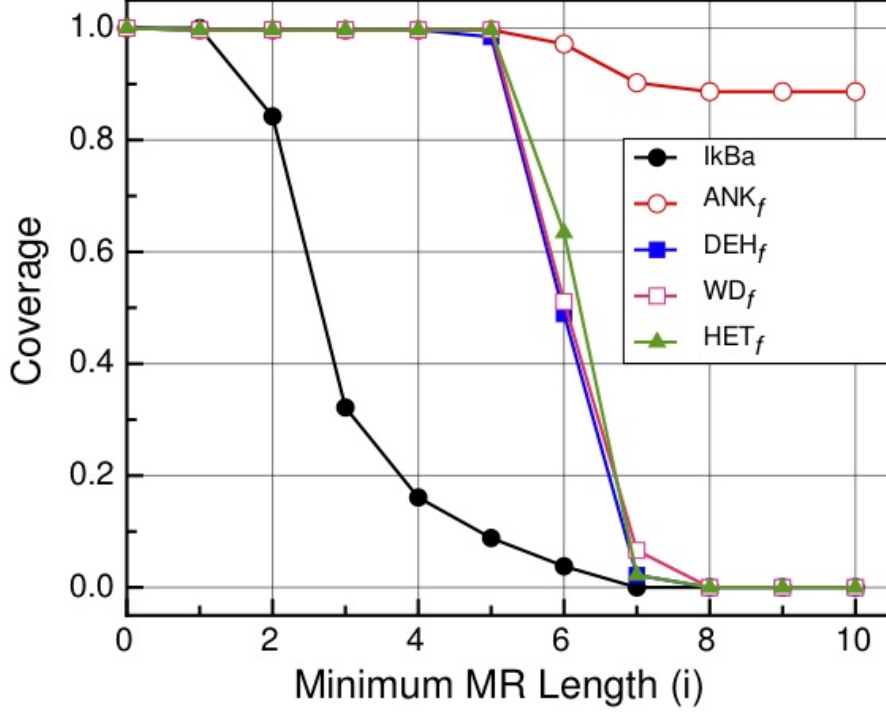


Figure 3: **Coverage of a trial sequence of IκBα using different MR sets.** The maximal repeats (MR) sets were computed from the sequence itself (black) or using groups of sequences derived from distinct families. Values come from applying $Coverage(IκBα, \mathcal{M}(t, i))$ function for $t = IκBα, ANK_f, DEH_f, WD_f, HET_f$ and $i = 0, \dots, 10$

There is a subtype of ANK proteins, which are synthetic constructs that are composed of (nearly) identical repetitions, for which, as expected, we detected long MRs in sequence. The molecules, such as DARPINs, OR264, OR266 and NRC, have a much larger coverage than natural ANKs, realized by their long perfect repeats (which are directly connected to the construction methods) [9,10] (see Table in Table S1).

The results we obtained for ANK_t were contrasted with results of two other protein families. WD-40 proteins (WD_t) are non-solenoid repetitive proteins with mainly β composition, that fold into a globular-like β -propeller fold. For these proteins, the distribution of MR lengths is similar to that of ANKs, with infrequent exact repeats larger than 6 residues (see Table in 3). Additionally we tested our program in a non-repetitive globular scaffold using members from

the Dehalogenase family (DEH_t). Results are shown in Table in 2. In general, the *coverage* function applied to DEH_t proteins goes to zero for lower i values than in the repeat protein families, indicating that the MRs in DEH_t proteins are shorter than the MRs in repeat proteins. The low coverage of the sequences may be consequence of their divergence during evolutionary time scales. Most of existing methods for repeat detection in protein sequences partially fail when proteins are too divergent respect a consensus sequence. However, the identification of the individual occurrences of repeats is simple to observe at the structural level. The higher conservation of the repetitive patterns in structures has been recently exploited to visually classify and annotate these kind of proteins [11]. Since protein sequences encode protein structures, we believe there must be a way to unravel the sequence repetitiveness despite the dissimilarity among the repeats.

Maximal repeats in families

As we have seen previously, long stretches of perfect repeats are infrequent in natural proteins, even for those which are known to fold into structures of recurrent structural motifs. Sequence-wise, repeats are known to be imperfect. Unfortunately, the methods that assume repeats to be degenerated fail to make a complete detection. Also these methods do not allow to conclude if some individual motifs actually occur or not. For instance, in ANKs, there are some specific sub-motifs that are characteristic of the family when looking at the statistical profile of ANK repeats, as a TPLH motif and variations of it; however, when looking at particular individual sequences it is hard to say whether they correspond to ANK instances or not. All possible variations of typical blocks should be represented in at least on member of the family. Sequence statistical profiles, usually assume that positions are independent. Therefore, when combining different amino acids at adjacent positions, blocks that are not representative of the family can be constructed, since natural covariations are not taken into account. The opposite, i.e natural occurring blocks that are a consequence of combinations of amino acids with low frequencies may not be detected as part of the motif. We overcome this problem by looking for natural occurring blocks in members of the family. This additionally solves the problem of position independence since these are implicitly used in the short repetitions.

Given a sequence s and a family f our method consists in finding the repetitions in the family f that have some occurrence in the sequence s . We first compute the sets $\mathcal{M}(t, i)$, where t is the concatenation of the sequences in f separated by pairwise different symbols, for all the possible values of values of i , namely i goes from 1 to $|s|$. We then compute the coverage made by the elements of $\mathcal{M}(t, i)$ on the sequence s using the *coverage*($s, \mathcal{M}(t, i)$) function. As example, Fig. 3 presents the coverage of the $\text{I}\kappa\text{B}\alpha$ protein considering sets of MRs from different families. The coverage was calculated by the *coverage*($\text{I}\kappa\text{B}\alpha, \mathcal{M}(t, i)$) function, using $t = \text{I}\kappa\text{B}\alpha$ alone, ANK_f , DEH_f , WD_f and HET_f datasets and $i = 0, \dots, 10$. The HET_f dataset is a selection of proteins from different families. We observe that, as the minimum MR length

increases above $i = 3$ the $\text{coverage}(\text{IkBa}, \mathcal{M}(\text{IkBa}, i))$ decays under 0.02 (black line), while the coverage remains close to 1 for MRs detected in larger datasets up to $i = 6$. The coverage only keeps significantly high for longer MRs when using the set of MRs obtained from the ANK family, to which the protein belongs. With these results, we computed the $\text{familiarity}(\text{IkBa}, t)$ function for $t = \text{IkBa}$ alone, ANK_f , DEH_f , WD_f and HET_f datasets. Although the definition of familiarity requires the values of $\text{coverage}(s, \mathcal{M}(t, i))$ for each i in $[0..|s|]$, in all the cases we analyzed it was enough to consider i just in $[0..10]$, because the coverage for larger values of i is negligible. Hereafter we consider the familiarity function with lengths $i \in [0..10]$. The maximum coverage is obtained for $\text{familiarity}(\text{IkBa}, \text{ANK}_f) = 9.57571$. familiarity function applied to IkBa together with other families have values less than 6.15 (see Table in 4, Uniprot ID = P25963). This function indicates that IkBa belongs to the ANK_f family. To verify if this hypothesis can be generalized, we also applied the previous familiarity function to each of the 223 test sequences for which the protein structure is known. These test sequences include 73 ANKs (ANK_t), 50 DEHs (DEH_t), 50 WD-40s (WD_t) and 50 randomly selected proteins that do not belong to the previous families (HET_t). For more details on how these sets were constructed see the section on Materials and Methods. Values of this function are shown in Table in 4. A global visualization of the values can be seen in Fig. 4. As for the IkBa protein, we observe that the familiarity function for the sequence s itself lays in between 2 and 4, except for designed ANKs that have higher values. These low values are a consequence of the low number of exact repeats in their sequence composition, regardless they belong to a repetitive or globular family. Even when repetitiveness is evident at the structural level, sequences from repetitive and globular proteins are indistinguishable in terms of the covering done by their own MRs. On the contrary, we observed a clear difference for the familiarity values for these sequences when evaluated in the context of families. For all proteins belonging to the ANK_t , WD_t and DEH_t the familiarity values are in a range from 6 to 10 when evaluated in the context of their own family, but drop to values around 6 when evaluated in the context of a family different to its own. One interpretation of these results is that protein families constitute ensembles where each of its members is composed of perfect repeats that are present in other members of the ensemble.

To our surprise, we were not able to see differences between the familiarity values of repeat families and globular families. Our hypothesis is that this high familiarity value is a common feature of protein families that are equilibrated ensembles whose members are mostly composed of exact repetitions ranging from dipeptides to decapeptides. This also suggests that natural proteins are built up from fragments longer than dipeptides but shorter than decapeptides, in line with the general ideas implemented by ‘fragment assembly’ of synthetic proteins [12].

There are however, some notable exceptions in the results of familiarity values in our experiments. In the case of ANK_t , protein $P14585$ is composed of more than 1400 residues, but its ANK region encompasses only about 200 amino acids. As a consequence of this, the coverage (and familiarity) obtained for this

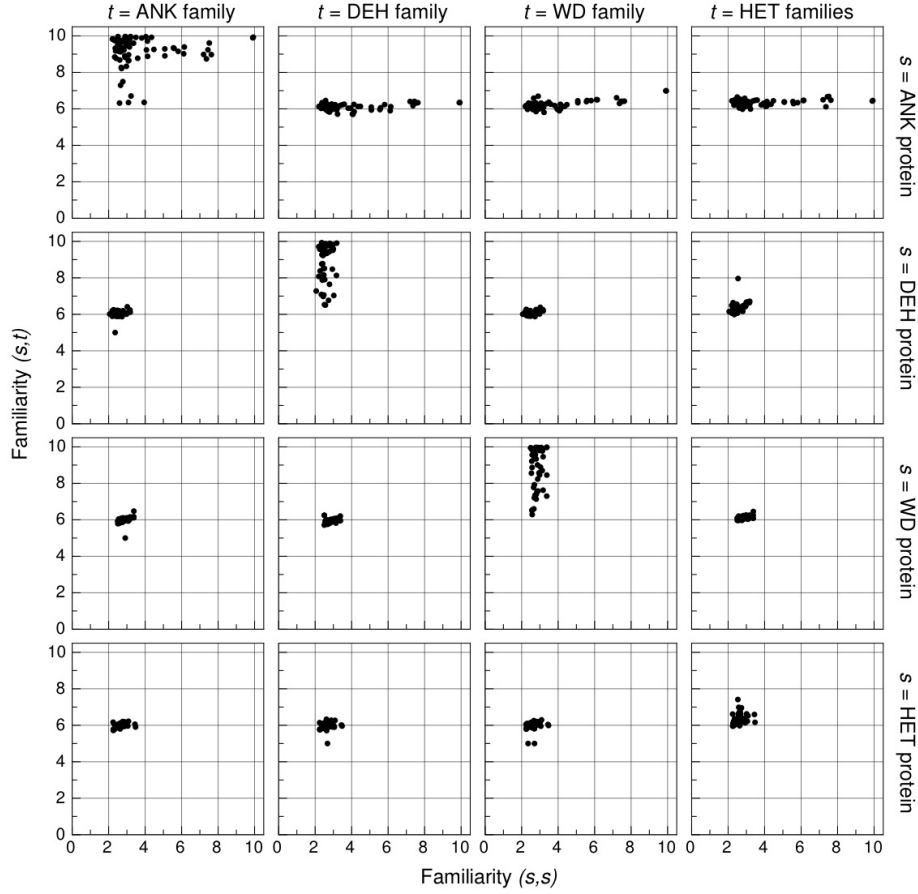


Figure 4: *familiarity* of 223 trial protein sequences was calculated using maximal repeats (MR) sets derived from distinct sequences. The x-axis denotes the *familiarity*(s, s) of the proteins, s , with MR set calculated from the sequence itself, the y-axis shows the *familiarity*(s, t) calculated with MR sets derived from distinct families, t .

sequence in the context of the ANK_f set does not display values significantly higher than for the other sets corresponding to foreign families.

Other exceptional cases within the ANK_t group of sequences that are not well explained by MRs found in the ANK_f set are proteins that fold into ANK-like structures but strongly differ from the rest of the family in their sequence patterns. These cases correspond to sequences $Q5ZSV0$ and $Q5ZXN6$ from *Legionella sp*, sequence $Q978J0$ from *Thermoplasma volcanium*, sequence $O22265$ which is the only protein from a plant in the dataset, and sequence $Q6IV60$ which is a viral protein. Except for the plant protein, all these cases are non-eukaryote proteins. The ANK motif is known to be particularly enriched

in eukaryotes and within specific eukaryote pathogens (including bacteria and viruses) that use ANK-like proteins to mimic their host counterparts and proceed with the infectious processes [13]. The origin of non-eukaryote ANK-like proteins has been discussed with no consensus about whether they correspond to horizontally transferred molecules with subsequent divergent evolution, or they originated by convergent evolutionary processes.

How are maximal repeats distributed in the families?

For each family dataset (ANK_f , DEH_f , WD_f and HET_f) we evaluated how its MRs are distributed within the proteins members of the family. We counted how many proteins in the family contain each of the MRs that are found in that family (Fig. 5A shows the case of ANK_f , and Fig. S1 shows the case for the remaining datasets). We observe that there is a large number of short MRs occurring in many different proteins (e.g. “TP” appears over 85% of ANK_f proteins), and a small number of long MRs occurring in just a few different proteins (e.g. “GNPFTPLHCAVINDHE” appears only in two proteins from ANK_f). The longest MR sequence (2,563 residues) has only two instances and appears in two very similar proteins (F1MVI7 and G3MYJ1).

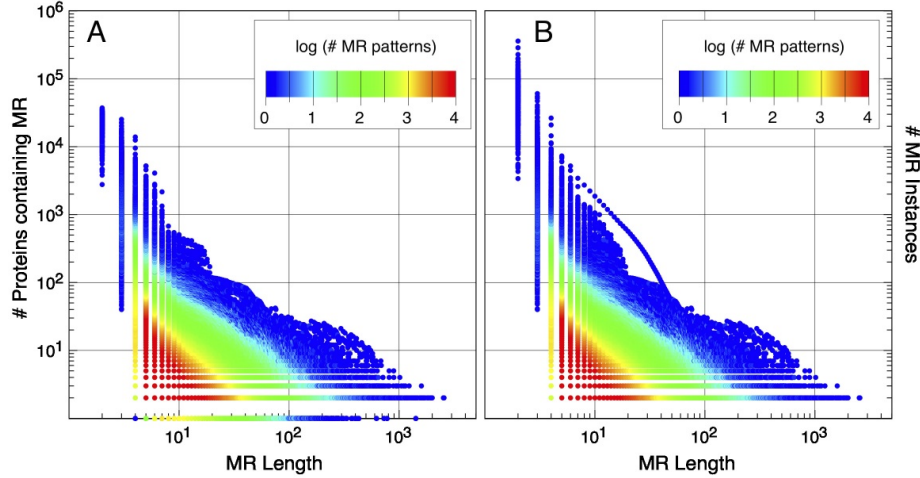


Figure 5: **The sequences of the ankyrin family (ANK_f) were used to calculate the maximal repeats (MR) set.** The distribution of the millions of MR found on the whole set is shown according to the length of the pattern. A) Number of different proteins that contain the MR pattern. B) Number of times each MR pattern is present in the whole dataset. The colorscale denotes the number of different MR patterns that occur at a particular coordinate.

Considering that MRs with lengths $i \geq 6$ generally are only found in the family’s own proteins, we focused on MRs corresponding to those i values. ANK_f has a total of 38,051 proteins but MRs larger than 6 residues do not

appear in all of them (the most popular MR of length 6 appears in 4,085 proteins, but in average MRs of this length appear in less than 1,000 proteins). Thus, there is no block larger or equal than six, common to the whole family. The coverage of each member of the ANK family by MRs in ANK_f comes from many different proteins. In this sense, the ANK proteins seem to be a mosaic of exact MRs that are spread along their whole sequence. The number of mismatches in individual sequences of a given family, found by pairwise alignments inside each sequence, vanishes dramatically if we consider the repeating blocks in other proteins from the family.

In ANK_f we observe that, starting from MRs of lengths $i \geq 6$, Figs. 5A and 5B are very similar. This shows that MRs occur at most once within each protein sequence. It also proves that long stretches of perfect repeats are infrequent in natural proteins, even for specific members that are known to fold into structures of recurrent structural motifs. However, there is a collection of recurring MRs that are spread along the members of a family than can be used to (partially) reconstruct any given sequence of the family.

The same analysis over other families (DEH_f and WD_f) shows similar results to those for ANK_f (see Fig. S1). We also considered a dataset of sequences constructed by scrambling the proteins of a given family (this dataset constructed by scrambling the amino acids of each sequence from HET_f dataset). The result differs completely from the results for actual families (Fig. S1). This is expected because scrambled sequences have less and shorter repeats. We made the same analysis for the HET_f dataset (Fig. S1). Although the HET_f has longer MRs than the scrambled protein family dataset, these MRs are notoriously shorter than the MRs in the ANK_f , DEH_f and WD_f families. This experiment gives evidence for the difference between sets of sequences that constitute an actual protein family and sets of proteins which do not constitute a family, as compared to sequences that do not correspond to actual proteins.

Towards a catalogue of repeats

We computed the set of MRs of length 6 or longer from the ANK_f dataset, this is $\mathcal{M}(ANK_f, 6)$. The minimum length value of 6 was selected to compare what we observe in small structural repetitions with the tiling methodology [3]. As a result we obtained 4,390,695 MRs with a length of 6 residues which exponentially decreases as the MRs length increases. The most frequent MRs, for instance TPLHLA and GADVNA (and their variants), coincide with the most popular motifs in the ANK HMM profile (Pfam ID: PF00023). We computed the proportion between instances of the MRs and the number of proteins containing them. The most well known motifs, have a proportion close to 1. However, we found several other motifs to be quite popular, as LISHGA, GHLDVV and ELLISH. They have a higher proportion between instances of the MRs and the number of proteins containing them (between 2 and 3), and they are conserved along repeat domains in the ANK_f dataset. The particularity of these motifs is that their occurrences are not evident when visually observing the sequence logo representation for the ANK HMM profile, because they are composed of

highly frequent amino acids at some positions and infrequent amino acids in others. The identified motifs respect the short length covariation in between positions, which is not taken into account in HMMs, in which the positions are assumed to be independent. Consequently, strategies like scanning sequences with HMM profiles need to apply a threshold to accept or not a subsequence as a hit. This can lead to spurious amino acid combinations producing false positives or false negative results. Using short exact sequences in order to look for MRs, considers implicitly the natural covariation among the residues that constitute them and at the same time allows us to avoid the use of thresholds.

Concluding Remarks

We posed the question: *How repetitive are natural repeat-proteins?* We committed to a mathematical definition of a repeat and found that long stretches of perfect repeats are infrequent in natural proteins, even for those which are known to fold into structures of recurrent structural motifs. However, we found that repeat proteins have abundant stretches of 6 amino acids or longer that are perfect repetitions in the reference family. We provided a systematic quantification for this repetitiveness.

Our solution finds all the maximal perfect repetitions, using no adjustable parameters. We use a reference family of protein sequences, that operates as a catalogue of all the possible variations that repeating blocks can adopt. We show that a large portion of each protein sequence can be described by short stretches of amino acids occurring in members of the reference family. Thus, each family determines an expected covering of its sequences by family repeats. This yields a measure of likelihood for any sequence to belong to a given family, quantified by the *familiarity* function. This function actually provides a classification method for proteins in families. The method could be used as a guiding tool in the design of synthetic proteins, establishing a minimum and a maximum value of a candidate sequence in relation to existing families.

The familiarity function can be implemented with an algorithm whose computational complexity is $O(n \log n)$, where n is the size of the protein sequence plus the size of the family dataset. This allows to compute the classification very efficiently.

This work is rooted in an exhaustive analysis of three natural protein families and two control families, taken as examples. The study can be extended to cover the complete protein universe or a substantial part of it. Moreover, the approach does not require a detailed curation of the sequences present in the families. We have limited our current work to the identification of MRs in families and to the computation of the familiarity function. Detailed statistical work remains to be done on MRs in families, such as the average distance between different occurrence of MRs inside the same protein sequence, the number of different MRs per length in each protein sequence. We also suggest to identify the subset of overlapping MRs (and the size of the overlap), the subset of non-overlapping MRs, the subsets of MRs that can be placed one after another, and the subset of MRs that exclude the occurrence of others. These statistics may yield relations

between maximal repeats with some known functional features and to some further conditions for the construction of synthetic proteins.

Materials and Methods

Protein family datasets

Ankyrin repeat protein (ANK_f) and WD40 repeat protein (WD_f) families datasets. From Uniprot Uniref0.9 we run hmmsearch from the hmmer suit for a specific HMM family taken from PFAM. Included only sequences that contain at least one hit for the specific family hmm. We excluded those protein sequences containing undefined or ambiguous residues (X,B,Z,J).

Haloacid Dehalogenase globular family dataset (DEH_f). A globular family was retrieved from the SFLD site (<http://sfld.rbvi.ucsf.edu/django/superfamily/3/>) from which we selected the Haloacid Dehalogenase superfamily. It was reduced to a 90% identity for non redundancy with cd-hit. Once reduced, the total number of residues in that family was 24,031,515 which was a shorter amount of residues when compared to ANK_f and WD_f datasets. In order to be fair with all the datasets and avoid a bias due to random matches product of the dataset size, we reduced the ANK_f and WD_f to have an equivalent size to the DEH_f ($\sim 24\text{K}$ residues).

Heterogeneous dataset (HET_f). We constructed a random dataset by taking a sample of proteins from Uniref0.9 in such a way that the total size in number of residues was equivalent to the other datasets and the selected proteins do not belong to any of the above mentioned families.

Scrambled heterogeneous dataset (HET_f scrambled). We constructed a new dataset, scrambling the amino acids of each sequence from HET_f dataset.

Protein test groups dataset

ANK test group dataset (ANK_t). We retrieved all the non redundant structures, 74 in total, from RepeatsDB [11].

WD40 test group dataset (WD_t). 50 Structures corresponding to members of the WD40 Protein Family, not included in the WD_f set, were randomly selected in to conform this group.

Haloacid Dehalogenase test group dataset (DEH_t). 50 Structures corresponding to members of the DEH Protein Family were randomly selected to conform this group. These structures were selected from the SFLD site, from those proteins that were not included when building the DEH_f set.

Globular Non Family test group dataset (HET_t). 50 Structures corresponding to a set of unrelated globular proteins was used to conform this group [14].

Repeat finding algorithm

The algorithm *findpat* [15], is the most current efficient algorithm to find exact repeats (it particularly well suited for very large inputs). The algorithm requires a parameter *ml* for the minimum length of a MR to be reported, it can be any value greater than or equal to 1. For the special case of *ml* equal to 0 *findpat* returns all possible blocks of the given sequence. To avoid the use of multiple different special symbols $\$_i$, for as many i as needed, we modified the program to have an unique special symbol $\$$ as a symbol that can not be part of MRs. The algorithm *findpat* runs in time $O(n \log n)$, where n is the length of the whole input (target sequence or sequences for the family of proteins).

Supporting Information

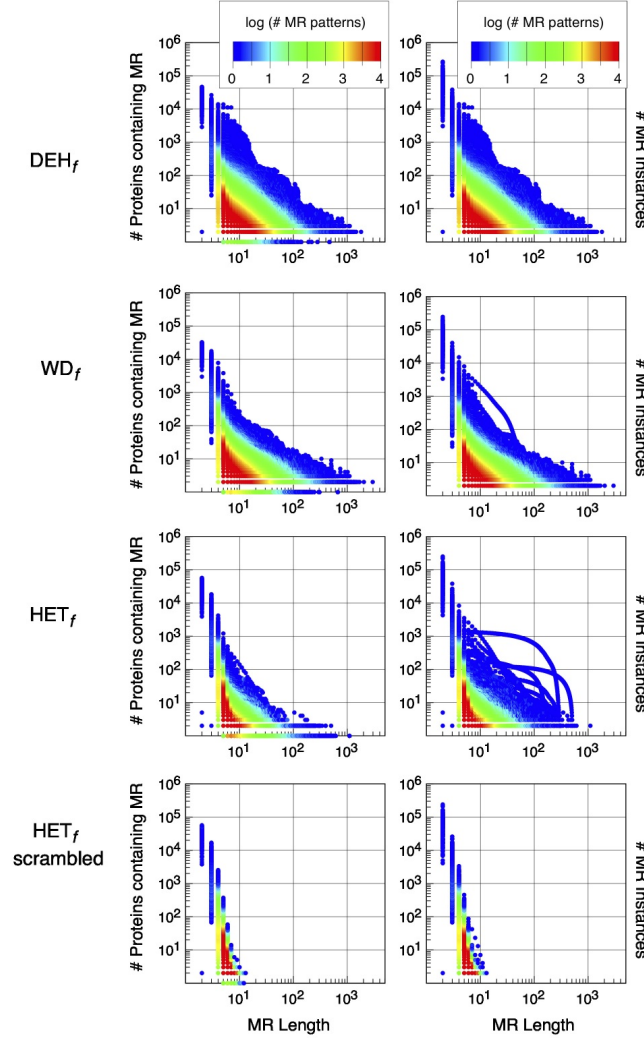


Figure S1. Maximal repeats (MR) distribution within the proteins members of the family. The sequences of distinct families were used to calculate the MR set. The distribution of the millions of MR found on the each set is shown according to the length of the pattern. On the left column, the number of different proteins that contain the MR pattern. On the right column, the number of time each MR pattern is present in the whole dataset. The colorscale denotes the number of different MR patterns that occur at a particular coordinate.

Table S1. Coverage of trial sequences of the ANK_t group. The values for the $coverage(s, \mathcal{M}(s, i))$ function for each sequence, s , name by the UniProt identifier was calculated for different minimum length of the maximal repeats (MR) from $i = 0 \dots 10$. Values truncated to two decimal places.

Uniprot ID (s)	$i = 0$	$i = 1$	$i = 2$	$i = 3$	$i = 4$	$i = 5$	$i = 6$	$i = 7$	$i = 8$	$i = 9$	$i = 10$
DARPIN-1D5	1.00	0.98	0.79	0.43	0.43	0.43	0.43	0.38	0.27	0.27	0.27
DARPIN-20	1.00	0.99	0.77	0.40	0.40	0.40	0.32	0.27	0.16	0.16	0.16
DARPIN-3ANK	1.00	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98	0.98
DARPIN-3CA1A2N	1.00	0.97	0.71	0.27	0.18	0.00	0.00	0.00	0.00	0.00	0.00
DARPIN-3CA1A2N-OH	1.00	0.97	0.75	0.32	0.23	0.10	0.00	0.00	0.00	0.00	0.00
DARPIN-3H10	1.00	0.99	0.80	0.67	0.60	0.56	0.56	0.52	0.36	0.36	0.36
DARPIN-4ANK	1.00	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99
DARPIN-AR-3A	1.00	1.00	0.78	0.49	0.49	0.49	0.40	0.32	0.23	0.23	0.23
DARPIN-AR-F8	1.00	0.99	0.80	0.55	0.50	0.50	0.50	0.43	0.29	0.29	0.29
DARPIN-E3-19	1.00	0.99	0.82	0.58	0.55	0.55	0.55	0.55	0.41	0.41	0.30
DARPIN-E3-5	1.00	0.99	0.85	0.60	0.56	0.51	0.51	0.51	0.29	0.29	0.29
DARPIN-H10-2-G3	1.00	0.99	0.80	0.37	0.32	0.32	0.16	0.11	0.00	0.00	0.00
DARPIN-NIIC-Mut4	1.00	0.95	0.72	0.20	0.08	0.00	0.00	0.00	0.00	0.00	0.00
DARPIN-NI3C	1.00	0.98	0.88	0.70	0.68	0.68	0.68	0.68	0.68	0.68	0.68
DARPIN-NI3C-Mut5	1.00	0.99	0.89	0.70	0.66	0.66	0.66	0.66	0.66	0.66	0.66
DARPIN-OFF7	1.00	1.00	0.79	0.50	0.50	0.50	0.50	0.49	0.36	0.26	0.26
E9ADW8	1.00	1.00	0.88	0.26	0.06	0.00	0.00	0.00	0.00	0.00	0.00
NRC	1.00	0.99	0.95	0.89	0.77	0.73	0.68	0.59	0.59	0.45	0.35
O14593	1.00	1.00	0.82	0.25	0.00	0.00	0.00	0.00	0.00	0.00	0.00
O22265	1.00	1.00	0.85	0.25	0.09	0.04	0.01	0.00	0.00	0.00	0.00
O35433	1.00	1.00	0.97	0.37	0.03	0.00	0.00	0.00	0.00	0.00	0.00
O75832	1.00	0.99	0.81	0.16	0.03	0.00	0.00	0.00	0.00	0.00	0.00
OR264	1.00	0.98	0.89	0.81	0.76	0.76	0.70	0.63	0.63	0.63	0.57
OR266	1.00	0.98	0.89	0.77	0.71	0.71	0.60	0.57	0.57	0.57	0.57
P07207	1.00	1.00	0.99	0.80	0.36	0.19	0.13	0.08	0.02	0.01	0.01
P09959	1.00	1.00	0.97	0.50	0.08	0.01	0.00	0.00	0.00	0.00	0.00
P14585	1.00	1.00	0.99	0.58	0.11	0.02	0.00	0.00	0.00	0.00	0.00
P16157	1.00	1.00	0.99	0.75	0.28	0.12	0.08	0.04	0.02	0.00	0.00
P20749	1.00	1.00	0.91	0.48	0.13	0.02	0.00	0.00	0.00	0.00	0.00
P25963	1.00	1.00	0.84	0.32	0.16	0.08	0.03	0.00	0.00	0.00	0.00
P42771	1.00	0.98	0.82	0.21	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P42773	1.00	0.98	0.77	0.06	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P46531	1.00	1.00	0.99	0.82	0.36	0.21	0.08	0.03	0.01	0.00	0.00
P46683	1.00	0.99	0.80	0.07	0.04	0.00	0.00	0.00	0.00	0.00	0.00
P50086	1.00	1.00	0.83	0.20	0.07	0.00	0.00	0.00	0.00	0.00	0.00
P55271	1.00	0.98	0.70	0.16	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P55273	1.00	1.00	0.83	0.23	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P58546	1.00	0.99	0.49	0.15	0.06	0.00	0.00	0.00	0.00	0.00	0.00
P62774	1.00	0.99	0.51	0.15	0.06	0.00	0.00	0.00	0.00	0.00	0.00
P62775	1.00	0.99	0.51	0.15	0.06	0.00	0.00	0.00	0.00	0.00	0.00
Q00420	1.00	1.00	0.88	0.28	0.06	0.00	0.00	0.00	0.00	0.00	0.00
Q01705	1.00	1.00	0.99	0.82	0.37	0.21	0.09	0.04	0.01	0.00	0.00
Q05823	1.00	1.00	0.97	0.51	0.08	0.03	0.00	0.00	0.00	0.00	0.00
Q13418	1.00	1.00	0.92	0.18	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Q13625	1.00	1.00	0.98	0.58	0.11	0.01	0.00	0.00	0.00	0.00	0.00
Q15027	1.00	1.00	0.96	0.43	0.07	0.00	0.00	0.00	0.00	0.00	0.00
Q5ZSV0	1.00	1.00	0.83	0.41	0.25	0.21	0.19	0.17	0.17	0.13	0.13
Q5ZXX6	1.00	1.00	0.98	0.50	0.08	0.01	0.00	0.00	0.00	0.00	0.00
Q60773	1.00	0.99	0.71	0.12	0.04	0.00	0.00	0.00	0.00	0.00	0.00
Q60778	1.00	1.00	0.90	0.36	0.18	0.09	0.05	0.00	0.00	0.00	0.00
Q63ZY3	1.00	1.00	0.97	0.51	0.09	0.02	0.01	0.01	0.00	0.00	0.00
Q6IV60	1.00	1.00	0.83	0.22	0.02	0.00	0.00	0.00	0.00	0.00	0.00
Q6PFX9	1.00	1.00	0.98	0.63	0.33	0.19	0.15	0.13	0.08	0.07	0.05
Q7SIG6	1.00	1.00	0.98	0.49	0.07	0.02	0.00	0.00	0.00	0.00	0.00
Q838Q8	1.00	1.00	0.83	0.31	0.03	0.00	0.00	0.00	0.00	0.00	0.00
Q8IUH5	1.00	1.00	0.94	0.32	0.01	0.00	0.00	0.00	0.00	0.00	0.00

Q8TDY4	1.00	1.00	0.97	0.47	0.04	0.00	0.00	0.00	0.00	0.00	0.00
Q8WUF5	1.00	1.00	0.96	0.56	0.21	0.05	0.02	0.01	0.01	0.01	0.00
Q90623	1.00	1.00	0.98	0.62	0.25	0.08	0.03	0.00	0.00	0.00	0.00
Q91WD2	1.00	1.00	0.97	0.30	0.02	0.01	0.01	0.00	0.00	0.00	0.00
Q92882	1.00	1.00	0.69	0.13	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q96DX5	1.00	1.00	0.87	0.29	0.05	0.00	0.00	0.00	0.00	0.00	0.00
Q96NW4	1.00	1.00	0.98	0.46	0.10	0.06	0.03	0.02	0.00	0.00	0.00
Q978J0	1.00	0.98	0.84	0.26	0.04	0.00	0.00	0.00	0.00	0.00	0.00
Q99728	1.00	1.00	0.96	0.35	0.05	0.02	0.00	0.00	0.00	0.00	0.00
Q9DFS3	1.00	1.00	0.98	0.43	0.04	0.00	0.00	0.00	0.00	0.00	0.00
Q9H2K2	1.00	1.00	0.98	0.60	0.32	0.23	0.21	0.17	0.15	0.10	0.07
Q9H9B1	1.00	1.00	0.99	0.53	0.09	0.00	0.00	0.00	0.00	0.00	0.00
Q9H9E1	1.00	1.00	0.85	0.19	0.10	0.03	0.00	0.00	0.00	0.00	0.00
Q9HBA0	1.00	1.00	0.97	0.38	0.03	0.01	0.00	0.00	0.00	0.00	0.00
Q9WUD2	1.00	1.00	0.96	0.43	0.07	0.00	0.00	0.00	0.00	0.00	0.00
Q9Y5S1	1.00	1.00	0.96	0.42	0.06	0.00	0.00	0.00	0.00	0.00	0.00
Q9Z2X2	1.00	1.00	0.77	0.18	0.03	0.00	0.00	0.00	0.00	0.00	0.00

Table S2. Coverage of trial sequences of the DEH_t group. The values for the $\text{coverage}(s, \mathcal{M}(s, i))$ function for each sequence, s , name by the UniProt identifier was calculated for different minimum length of the maximal repeats (MR) from $i = 0 \dots 10$. Values truncated to two decimal places.

Uniprot ID (s)	$i = 0$	$i = 1$	$i = 2$	$i = 3$	$i = 4$	$i = 5$	$i = 6$	$i = 7$	$i = 8$	$i = 9$	$i = 10$
A5LN19	1.00	1.00	0.83	0.23	0.07	0.03	0.00	0.00	0.00	0.00	0.00
B0A4S9	1.00	0.98	0.77	0.17	0.00	0.00	0.00	0.00	0.00	0.00	0.00
B2Z3V8	1.00	0.99	0.69	0.15	0.00	0.00	0.00	0.00	0.00	0.00	0.00
B4A833	1.00	1.00	0.79	0.16	0.00	0.00	0.00	0.00	0.00	0.00	0.00
B4ABS1	1.00	1.00	0.81	0.21	0.03	0.00	0.00	0.00	0.00	0.00	0.00
C2JJ26	1.00	1.00	0.88	0.21	0.09	0.00	0.00	0.00	0.00	0.00	0.00
C6IG92	1.00	0.99	0.56	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
C7RF86	1.00	1.00	0.88	0.27	0.04	0.02	0.00	0.00	0.00	0.00	0.00
D4FVT8	1.00	1.00	0.69	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
D4V4M5	1.00	0.99	0.71	0.20	0.03	0.00	0.00	0.00	0.00	0.00	0.00
D7IJ01	1.00	0.99	0.80	0.17	0.03	0.00	0.00	0.00	0.00	0.00	0.00
D8FP15	1.00	0.99	0.77	0.11	0.00	0.00	0.00	0.00	0.00	0.00	0.00
G9RLJ0	1.00	1.00	0.78	0.09	0.00	0.00	0.00	0.00	0.00	0.00	0.00
K2T267	1.00	0.99	0.72	0.13	0.00	0.00	0.00	0.00	0.00	0.00	0.00
M2DKS0	1.00	0.99	0.89	0.22	0.04	0.00	0.00	0.00	0.00	0.00	0.00
M4SEQ9	1.00	1.00	0.96	0.47	0.05	0.00	0.00	0.00	0.00	0.00	0.00
O08575	1.00	1.00	0.91	0.31	0.06	0.00	0.00	0.00	0.00	0.00	0.00
O15305	1.00	0.99	0.76	0.20	0.03	0.00	0.00	0.00	0.00	0.00	0.00
O29777	1.00	1.00	0.97	0.55	0.09	0.02	0.01	0.00	0.00	0.00	0.00
O32125	1.00	0.99	0.79	0.09	0.02	0.02	0.00	0.00	0.00	0.00	0.00
O32220	1.00	1.00	0.98	0.51	0.10	0.01	0.01	0.01	0.01	0.00	0.00
O59346	1.00	1.00	0.78	0.12	0.00	0.00	0.00	0.00	0.00	0.00	0.00
O67920	1.00	1.00	0.74	0.23	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P05023	1.00	1.00	0.97	0.30	0.08	0.01	0.00	0.00	0.00	0.00	0.00
P06685	1.00	1.00	0.99	0.43	0.05	0.00	0.00	0.00	0.00	0.00	0.00
P0AE22	1.00	0.99	0.72	0.12	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P20649	1.00	1.00	0.98	0.42	0.03	0.01	0.01	0.00	0.00	0.00	0.00
P35670	1.00	0.99	0.71	0.04	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P78330	1.00	0.99	0.74	0.11	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P94592	1.00	1.00	0.83	0.08	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q04656	1.00	0.96	0.52	0.13	0.06	0.06	0.00	0.00	0.00	0.00	0.00
Q11S56	1.00	0.99	0.76	0.14	0.02	0.00	0.00	0.00	0.00	0.00	0.00
Q2T109	1.00	0.98	0.67	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q3UGR5	1.00	1.00	0.83	0.24	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q5EBQ9	1.00	0.99	0.73	0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q5SJK3	1.00	0.99	0.90	0.39	0.18	0.03	0.00	0.00	0.00	0.00	0.00
Q60048	1.00	1.00	0.97	0.44	0.02	0.00	0.00	0.00	0.00	0.00	0.00
Q7ADF8	1.00	1.00	0.75	0.12	0.07	0.00	0.00	0.00	0.00	0.00	0.00
Q7WG29	1.00	1.00	0.62	0.23	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q8K7R3	1.00	0.99	0.85	0.24	0.03	0.00	0.00	0.00	0.00	0.00	0.00
Q8L1N9	1.00	0.99	0.74	0.25	0.03	0.00	0.00	0.00	0.00	0.00	0.00
Q8TBE9	1.00	1.00	0.80	0.13	0.05	0.02	0.00	0.00	0.00	0.00	0.00
Q96X90	1.00	1.00	0.85	0.20	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q96XE7	1.00	1.00	0.83	0.13	0.03	0.00	0.00	0.00	0.00	0.00	0.00
Q98I56	1.00	0.99	0.75	0.17	0.03	0.00	0.00	0.00	0.00	0.00	0.00
Q9D020	1.00	0.99	0.85	0.19	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q9JLV6	1.00	1.00	0.93	0.32	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Q9X0Y1	1.00	1.00	0.85	0.25	0.12	0.04	0.00	0.00	0.00	0.00	0.00
T0QBN5	1.00	0.99	0.79	0.16	0.03	0.00	0.00	0.00	0.00	0.00	0.00
U8H1V1	1.00	1.00	0.73	0.15	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Table S3. Coverage of trial sequences of the WD_t group. The values for the $coverage(s, \mathcal{M}(s, i))$ function for each sequence, s , name by the UniProt identifier was calculated for different minimum length of the maximal repeats (MR) from $i = 0 \dots 10$. Values truncated to two decimal places.

Uniprot ID (s)	$i = 0$	$i = 1$	$i = 2$	$i = 3$	$i = 4$	$i = 5$	$i = 6$	$i = 7$	$i = 8$	$i = 9$	$i = 10$
A6ZU46	1.00	1.00	0.98	0.44	0.04	0.01	0.00	0.00	0.00	0.00	0.00
O14727	1.00	1.00	0.99	0.52	0.08	0.03	0.00	0.00	0.00	0.00	0.00
O24456	1.00	1.00	0.85	0.38	0.11	0.08	0.04	0.04	0.00	0.00	0.00
O75530	1.00	1.00	0.90	0.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00
O76071	1.00	0.99	0.85	0.36	0.17	0.12	0.07	0.04	0.00	0.00	0.00
O88879	1.00	1.00	0.99	0.53	0.09	0.00	0.00	0.00	0.00	0.00	0.00
O89053	1.00	1.00	0.90	0.27	0.08	0.02	0.00	0.00	0.00	0.00	0.00
P07834	1.00	1.00	0.97	0.49	0.15	0.04	0.01	0.00	0.00	0.00	0.00
P16649	1.00	1.00	0.97	0.52	0.22	0.07	0.04	0.01	0.01	0.00	0.00
P26449	1.00	1.00	0.87	0.17	0.02	0.00	0.00	0.00	0.00	0.00	0.00
P36037	1.00	1.00	0.96	0.39	0.03	0.00	0.00	0.00	0.00	0.00	0.00
P38011	1.00	1.00	0.79	0.39	0.14	0.03	0.00	0.00	0.00	0.00	0.00
P38262	1.00	1.00	0.93	0.36	0.04	0.00	0.00	0.00	0.00	0.00	0.00
P38968	1.00	1.00	0.98	0.61	0.17	0.06	0.02	0.01	0.00	0.00	0.00
P40217	1.00	1.00	0.89	0.21	0.06	0.00	0.00	0.00	0.00	0.00	0.00
P46680	1.00	1.00	0.94	0.36	0.06	0.00	0.00	0.00	0.00	0.00	0.00
P53011	1.00	1.00	0.87	0.18	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P53196	1.00	1.00	0.86	0.16	0.03	0.00	0.00	0.00	0.00	0.00	0.00
P54311	1.00	1.00	0.87	0.28	0.08	0.02	0.00	0.00	0.00	0.00	0.00
P55735	1.00	1.00	0.85	0.26	0.13	0.00	0.00	0.00	0.00	0.00	0.00
P61964	1.00	0.99	0.87	0.43	0.23	0.14	0.10	0.08	0.00	0.00	0.00
P61965	1.00	0.99	0.87	0.43	0.23	0.14	0.10	0.08	0.00	0.00	0.00
P62871	1.00	1.00	0.87	0.28	0.08	0.02	0.00	0.00	0.00	0.00	0.00
P62881	1.00	1.00	0.87	0.30	0.02	0.00	0.00	0.00	0.00	0.00	0.00
P63005	1.00	1.00	0.89	0.34	0.11	0.04	0.04	0.04	0.04	0.04	0.00
P63244	1.00	1.00	0.87	0.31	0.08	0.03	0.03	0.00	0.00	0.00	0.00
P78406	1.00	1.00	0.85	0.14	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P78774	1.00	1.00	0.91	0.22	0.05	0.00	0.00	0.00	0.00	0.00	0.00
P78972	1.00	1.00	0.95	0.31	0.03	0.00	0.00	0.00	0.00	0.00	0.00
Q02793	1.00	1.00	0.87	0.27	0.02	0.00	0.00	0.00	0.00	0.00	0.00
Q03774	1.00	1.00	0.91	0.30	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Q04491	1.00	0.99	0.87	0.27	0.02	0.00	0.00	0.00	0.00	0.00	0.00
Q04724	1.00	1.00	0.96	0.40	0.07	0.00	0.00	0.00	0.00	0.00	0.00
Q05583	1.00	1.00	0.86	0.24	0.05	0.03	0.00	0.00	0.00	0.00	0.00
Q09028	1.00	1.00	0.90	0.29	0.08	0.02	0.00	0.00	0.00	0.00	0.00
Q11176	1.00	1.00	0.97	0.40	0.07	0.00	0.00	0.00	0.00	0.00	0.00
Q13216	1.00	1.00	0.88	0.26	0.04	0.00	0.00	0.00	0.00	0.00	0.00
Q16576	1.00	1.00	0.89	0.23	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Q24572	1.00	1.00	0.90	0.21	0.06	0.02	0.00	0.00	0.00	0.00	0.00
Q24D42	1.00	1.00	0.86	0.11	0.02	0.02	0.00	0.00	0.00	0.00	0.00
Q2YDS1	1.00	1.00	0.92	0.33	0.01	0.01	0.00	0.00	0.00	0.00	0.00
Q58CQ2	1.00	1.00	0.86	0.19	0.02	0.00	0.00	0.00	0.00	0.00	0.00
Q6CN23	1.00	1.00	0.84	0.18	0.04	0.00	0.00	0.00	0.00	0.00	0.00
Q8LNY6	1.00	1.00	0.86	0.28	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q921E6	1.00	1.00	0.90	0.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q92466	1.00	1.00	0.89	0.13	0.03	0.00	0.00	0.00	0.00	0.00	0.00
Q969H0	1.00	1.00	0.95	0.49	0.13	0.09	0.00	0.00	0.00	0.00	0.00
Q96MX6	1.00	1.00	0.84	0.19	0.02	0.00	0.00	0.00	0.00	0.00	0.00
Q9GZS3	1.00	1.00	0.90	0.29	0.09	0.03	0.03	0.00	0.00	0.00	0.00
Q9Y297	1.00	1.00	0.93	0.35	0.10	0.01	0.00	0.00	0.00	0.00	0.00

Table S4. Values of *familiarity* function for several proteins and families. Values of *familiarity*(s, t) function for s proteins from ANK $_t$, DEH $_t$, HET $_t$ and WD $_t$ test group dataset and $t=s$, ANK $_f$, DEH $_f$, HET $_f$ and WD $_f$.

Uniprot ID (s)	Test Group	familiarity (s,s)	familiarity (s,ANK $_f$)	familiarity (s,DEH $_f$)	familiarity (s,HET $_f$)	familiarity (s,WD $_f$)
DARPIN-1D5	ANK $_t$	5.07600	9.28800	6.09600	6.38400	6.44000
DARPIN-20	ANK $_t$	4.47984	9.25806	6.13306	6.43952	6.22984
DARPIN-3ANK	ANK $_t$	9.90110	9.89560	6.34066	6.42857	6.98901
DARPIN-3CA1A2N	ANK $_t$	2.65909	9.13068	6.25568	6.52841	6.58523
DARPIN-3CA1A2N-OH	ANK $_t$	2.90625	8.82292	6.26562	6.57813	6.69271
DARPIN-3H10	ANK $_t$	6.14615	9.39231	6.11923	6.46538	6.49615
DARPIN-4ANK	ANK $_t$	9.92857	9.92857	6.34524	6.45635	6.98810
DARPIN-AR-3A	ANK $_t$	5.08065	8.90645	5.93548	6.36774	6.33548
DARPIN-AR-F8	ANK $_t$	5.55063	9.34494	5.95886	6.40190	6.39557
DARPIN-E3-19	ANK $_t$	6.11290	9.01935	5.89677	6.45806	6.50323
DARPIN-E3-5	ANK $_t$	5.80818	9.15409	6.23270	6.33962	6.45283
DARPIN-H10-2-G3	ANK $_t$	3.59274	8.77419	6.25403	6.47984	6.25403
DARPIN-NIIC-Mut4	ANK $_t$	2.50000	9.20652	6.26630	6.64674	6.25543
DARPIN-NI3C	ANK $_t$	7.51623	9.61039	6.32143	6.67857	6.41234
DARPIN-NI3C-Mut5	ANK $_t$	7.44268	9.23567	6.40764	6.66242	6.40764
DARPIN-OFF7	ANK $_t$	5.58599	9.31847	6.05732	6.28662	6.45860
E9ADW8	ANK $_t$	2.71111	8.21250	6.04861	6.18750	5.97917
NRC	ANK $_t$	7.36087	8.73913	6.17391	6.11304	6.29565
O14593	ANK $_t$	2.58462	9.23077	6.07885	6.37115	6.14038
O22265	ANK $_t$	2.77614	7.49330	6.12601	6.36997	6.32976
O35433	ANK $_t$	2.88425	8.90155	5.96957	6.17959	6.03640
O75832	ANK $_t$	2.51106	9.96018	6.01549	6.24558	6.09513
OR264	ANK $_t$	7.63018	8.97337	6.33728	6.47337	6.42012
OR266	ANK $_t$	7.20414	8.98225	6.40237	6.49704	6.60947
P07207	ANK $_t$	4.13559	8.88124	5.84221	6.17888	5.99649
P09959	ANK $_t$	3.07659	8.63636	6.06102	6.19552	6.08593
P14585	ANK $_t$	3.22638	6.70329	5.71099	5.98880	5.80616
P16157	ANK $_t$	3.81366	9.88676	6.03615	6.21425	6.17916
P20749	ANK $_t$	3.06388	9.61013	6.15969	6.37996	6.31608
P25963	ANK $_t$	2.95110	9.57571	5.98423	6.14196	6.06309
P42771	ANK $_t$	2.53526	9.59295	6.36859	6.56090	6.29167
P42773	ANK $_t$	2.33036	8.84226	6.02679	6.31250	6.18750
P46531	ANK $_t$	4.04090	9.95362	5.71820	6.17143	5.91781
P46683	ANK $_t$	2.40750	8.77000	6.05250	6.23750	6.15750
P50086	ANK $_t$	2.60965	8.67982	5.94079	6.05482	6.02412
P55271	ANK $_t$	2.36154	9.32308	6.25769	6.49615	6.25000
P55273	ANK $_t$	2.57229	9.14759	6.45482	6.50904	6.26807
P58546	ANK $_t$	2.20763	9.82627	6.12288	6.43644	6.13136
P62774	ANK $_t$	2.23305	9.82627	6.13136	6.43644	6.16525
P62775	ANK $_t$	2.23305	9.82627	6.13136	6.43644	6.16525
Q00420	ANK $_t$	2.73760	9.67885	6.09661	6.29504	6.18277
Q01705	ANK $_t$	4.07171	9.23252	5.70170	6.12999	5.89648
Q05823	ANK $_t$	3.10324	8.65385	6.07018	6.25371	6.07152
Q13418	ANK $_t$	2.62168	9.74889	5.94580	6.05642	5.97456
Q13625	ANK $_t$	3.19947	9.96144	6.00133	6.28324	6.09087
Q15027	ANK $_t$	2.97432	9.92365	6.05068	6.32905	6.16824
Q5ZSV0	ANK $_t$	3.94565	6.35462	6.03940	6.30842	5.98777
Q5ZXX6	ANK $_t$	3.08588	6.34721	6.02529	6.26554	6.03793
Q60773	ANK $_t$	2.38253	9.17470	6.34036	6.36446	6.31627
Q60778	ANK $_t$	3.09331	8.96518	6.22841	6.40111	6.21170
Q63ZY3	ANK $_t$	3.14160	9.39424	6.13043	6.36193	6.25264
Q6IV60	ANK $_t$	2.59507	6.31514	6.05106	6.14965	5.97711
Q6PFX9	ANK $_t$	4.12500	9.71477	6.24356	6.40038	6.24811
Q7SIG6	ANK $_t$	3.06994	9.54593	5.99426	6.19468	6.08403
Q838Q8	ANK $_t$	2.68905	8.26866	6.04975	6.24378	6.07960
Q8IUH5	ANK $_t$	2.78956	9.77532	5.82674	5.98022	5.85047
Q8TDY4	ANK $_t$	2.99612	9.68328	6.07752	6.23256	6.19712

Q8WUF5	ANK _t	3.36353	9.60145	6.17935	6.43176	6.28140
Q90623	ANK _t	3.49203	9.91833	6.22759	6.47062	6.36504
Q91WD2	ANK _t	2.83700	9.22696	5.98900	6.20770	5.99312
Q92882	ANK _t	2.32243	9.75000	6.12850	6.20327	5.97430
Q96DX5	ANK _t	2.72109	9.26361	5.86565	6.12755	6.07313
Q96NW4	ANK _t	3.17714	9.86667	5.94238	6.15095	6.07000
Q978J0	ANK _t	2.65344	7.29101	6.13757	6.23810	6.05820
Q99728	ANK _t	2.90669	9.96589	6.01030	6.12098	6.08623
Q9DFS3	ANK _t	2.96596	9.47300	6.04049	6.18369	6.03228
Q9H2K2	ANK _t	4.34991	9.92153	6.12650	6.24914	6.13593
Q9H9B1	ANK _t	3.11864	9.67296	6.01194	6.16525	6.09592
Q9H9E1	ANK _t	2.69169	9.37380	5.88498	6.17252	6.14058
Q9HBA0	ANK _t	2.91102	9.74971	6.01148	6.14351	5.98737
Q9WUD2	ANK _t	2.97175	8.33180	5.98817	6.17740	6.00920
Q9Y5S1	ANK _t	2.95812	9.47709	6.00196	6.20746	5.99804
Q9Z2X2	ANK _t	2.49567	9.52597	6.06494	6.22078	6.12121
A5LN19	DEH _t	2.67899	6.05447	9.83463	6.26459	6.09339
B0A4S9	DEH _t	2.44253	6.02586	9.64368	6.35920	5.94540
B2Z3V8	DEH _t	2.33958	5.96458	7.08542	5.98958	5.94792
B4A833	DEH _t	2.46610	5.99322	8.15085	6.22034	5.97966
B4ABS1	DEH _t	2.56400	5.89000	9.87400	6.17800	6.06200
C2JJ26	DEH _t	2.68750	6.12305	9.38672	6.29492	6.07227
C6IG92	DEH _t	2.05755	6.01439	7.27698	6.15108	6.00719
C7RF86	DEH _t	2.73298	5.87304	6.76702	6.29974	5.87827
D4FVT8	DEH _t	2.19787	5.89362	8.07872	6.06809	5.99574
D4V4M5	DEH _t	2.45287	5.94467	8.49795	6.28893	5.96516
D7IJ01	DEH _t	2.50581	5.94767	8.51550	6.41279	6.00969
D8FP15	DEH _t	2.39331	6.10460	7.87657	6.33891	6.12971
G9RLJ0	DEH _t	2.37218	5.90414	9.27256	6.14850	5.91165
K2T267	DEH _t	2.35754	6.01117	9.72067	6.43017	6.16201
M2DKS0	DEH _t	2.65175	6.03113	9.75681	6.29572	6.11284
M4SEQ9	DEH _t	2.99457	6.07677	9.59375	6.65353	6.17867
O08575	DEH _t	2.80263	6.06297	9.89098	6.16071	6.05357
O15305	DEH _t	2.49390	5.89634	9.65854	6.16057	5.90447
O29777	DEH _t	3.16667	6.24067	8.13184	6.63619	6.25062
O32125	DEH _t	2.43045	5.90414	9.22556	6.09962	6.05451
O32220	DEH _t	3.18080	6.11534	9.90337	6.71384	6.18516
O59346	DEH _t	2.41286	6.04149	8.77801	6.26556	5.92116
O67920	DEH _t	2.47546	6.22086	7.06135	6.55215	6.20245
P05023	DEH _t	2.87004	6.05433	9.72981	6.49046	6.05727
P06685	DEH _t	2.97801	6.00880	9.82551	6.48876	6.02151
P0AE22	DEH _t	2.35443	6.00000	9.87764	6.17722	6.11392
P20649	DEH _t	2.97102	6.03267	9.51106	6.55321	6.03793
P35670	DEH _t	2.25532	6.05674	9.57092	6.34752	6.26950
P78330	DEH _t	2.36000	6.03111	9.92889	6.24000	6.05778
P94592	DEH _t	2.41579	6.03158	9.44737	6.24912	6.07719
Q04656	DEH _t	2.27222	6.25000	8.37778	6.63889	6.23889
Q11S56	DEH _t	2.44170	5.91519	6.98057	6.18728	6.03534
Q2T109	DEH _t	2.19519	6.19251	9.71123	6.48663	6.14439
Q3UGR5	DEH _t	2.57469	6.19087	9.45021	6.40664	6.09129
Q5EBQ9	DEH _t	2.28538	5.95519	9.73585	6.05896	5.92217
Q5SJQ3	DEH _t	3.02124	6.41313	7.03282	6.67181	6.38224
Q60048	DEH _t	2.94304	6.06610	8.47468	6.42194	6.09564
Q7ADF8	DEH _t	2.45045	6.10135	9.78829	6.43919	6.18694
Q7WQ29	DEH _t	2.36034	6.02235	8.75978	6.27933	6.08939
Q8K7R3	DEH _t	2.63386	5.99409	9.34252	6.28150	6.04921
Q8L1N9	DEH _t	2.52353	5.99216	7.90392	6.29804	6.13333
Q8TBE9	DEH _t	2.51481	6.07963	9.63704	6.23519	6.10926
Q96X90	DEH _t	2.56364	6.03864	6.50682	6.33864	6.08864
Q96XE7	DEH _t	2.50971	6.06553	6.53155	6.06553	5.91019
Q98I56	DEH _t	2.47005	6.05530	8.15207	6.41475	6.11982
Q9D020	DEH _t	2.54381	5.96073	9.45317	7.96073	5.98792
Q9JLV6	DEH _t	2.77969	6.06034	9.43774	6.24425	6.10057

Q9X0Y1	DEH _t	2.78704	6.19676	7.64583	6.45139	6.26157
T0QBN5	DEH _t	2.48256	5.96705	9.28876	6.40891	5.93605
U8H1V1	DEH _t	2.38293	5.98537	9.68780	6.21951	6.10732
B1MJ53	HET _t	2.57143	6.06656	6.15747	6.45942	6.07955
D3H0F7	HET _t	2.73485	6.06439	6.14520	6.29672	5.96843
E6Z0R3	HET _t	2.85146	6.09519	6.01151	6.20607	6.03033
F4AR88	HET _t	2.58306	6.05980	6.02990	6.98339	6.08970
O06961	HET _t	2.72886	6.03109	6.10323	6.95771	6.07587
O52806	HET _t	2.35366	5.92195	6.07805	6.36098	6.00000
O58456	HET _t	2.52453	6.04528	6.13585	6.24151	6.04151
P00437	HET _t	2.26569	5.74059	5.76569	6.10460	5.90795
P00693	HET _t	2.74658	5.95548	6.01256	6.29795	6.03767
P00772	HET _t	2.46617	5.89286	5.93421	6.17105	5.91165
P00800	HET _t	2.79197	6.02281	5.94982	6.20529	6.08120
P00918	HET _t	2.41346	5.88654	5.88269	6.07500	5.93654
P02883	HET _t	2.25604	5.78261	5.78744	5.97101	5.80676
P09211	HET _t	2.49524	6.02143	5.96905	6.27381	5.97381
P0A6C8	HET _t	2.61822	6.09884	6.33140	6.66473	6.19961
P0A8M3	HET _t	2.70093	5.90576	5.89486	6.37305	5.80763
P0C0Y9	HET _t	2.53571	5.91396	5.93019	7.41234	6.06981
P0C512	HET _t	2.67610	5.88050	6.00000	6.87002	6.01468
P23472	HET _t	2.58360	6.07395	5.99035	6.18650	5.96463
P23904	HET _t	2.32700	5.78059	5.80591	5.98734	5.89873
P26663	HET _t	3.44219	6.05797	6.01412	6.59169	6.04336
P27448	HET _t	3.01394	6.09429	5.99734	6.62351	6.13944
P29476	HET _t	3.05353	5.96011	5.89923	6.22113	5.94822
P32169	HET _t	2.43431	5.97263	5.83029	6.18431	5.93248
P35202	HET _t	2.46865	5.98433	5.95611	6.15361	5.89655
P37352	HET _t	2.85831	5.93677	6.14286	6.27166	6.03747
P46154	HET _t	2.68296	6.07519	6.07769	6.62155	6.07519
P50586	HET _t	2.77129	6.20594	6.07723	6.32079	6.20000
P61086	HET _t	2.24500	6.16750	6.14250	6.61250	6.05750
P69834	HET _t	2.49338	6.04470	6.11424	6.30960	6.14735
Q26997	HET _t	2.51522	5.87174	5.86739	6.20217	5.92826
Q3IWB0	HET _t	3.08891	6.21797	6.26960	6.52008	6.29446
Q51723	HET _t	2.68750	5.94174	5.96716	6.24470	5.82945
Q54727	HET _t	2.93687	6.01435	6.01148	6.13343	6.02296
Q5TA50	HET _t	2.29907	6.06776	6.09579	6.21729	6.10047
Q5TLG6	HET _t	2.25446	5.71652	5.75223	5.94866	5.78795
Q6DLV0	HET _t	3.47434	5.90398	5.95619	6.16062	5.98982
Q6G441	HET _t	2.62381	6.08690	6.14405	6.73571	6.14881
Q70C53	HET _t	2.64941	5.95118	5.86538	6.02515	5.83284
Q873X9	HET _t	2.76790	6.00924	5.93533	6.25173	6.18476
Q8A7T5	HET _t	2.70487	6.09939	5.96552	6.42394	6.00000
Q8DCF5	HET _t	2.55389	5.94461	5.98653	6.62575	5.94461
Q8TX37	HET _t	2.88268	6.18575	6.27793	6.38128	6.19693
Q97DM1	HET _t	2.62946	5.79737	5.70544	5.97373	5.92120
Q97VM5	HET _t	2.67969	6.12370	6.19141	6.36849	6.19401
Q9IFX1	HET _t	2.94501	5.97251	5.90729	6.18734	6.05946
Q9KF16	HET _t	2.55152	5.92974	6.00234	6.08665	5.89930
Q9NUI1	HET _t	2.67123	6.12842	6.03253	6.69007	6.25514
Q9P286	HET _t	2.90334	6.14812	5.92629	6.34075	6.11822
Q9WZY5	HET _t	2.49187	5.90041	5.88415	6.27439	5.93699
A6ZU46	WD _t	2.98594	6.10686	5.99100	6.26434	8.46175
O14727	WD _t	3.13301	6.02123	5.91306	6.11098	9.77244
O24456	WD _t	3.03211	6.03364	6.06422	6.15596	8.88838
O75530	WD _t	2.50227	5.92971	6.24490	6.08617	9.93991
O76071	WD _t	3.14159	6.00885	5.82006	6.06490	9.83776
O88879	WD _t	3.12770	6.09848	5.94396	6.15452	8.69936
O89053	WD _t	2.79501	6.10629	5.96746	6.15401	9.33731
P07834	WD _t	3.17522	6.12195	6.09114	6.24390	7.62323
P16649	WD _t	3.38079	6.47546	6.20477	6.45512	8.45231

P26449	WD _t	2.56452	5.95894	5.93255	6.08211	6.51026
P36037	WD _t	2.89441	6.06713	6.01958	6.16783	7.57832
P38011	WD _t	2.86991	6.05016	5.88088	6.19436	9.00940
P38262	WD _t	2.84019	6.04860	6.01682	6.23178	7.55140
P38968	WD _t	3.37510	6.17203	5.97486	6.25373	7.29929
P40217	WD _t	2.67867	5.92507	5.75216	6.10951	9.53458
P46680	WD _t	2.88049	6.02602	5.94959	6.09268	8.23171
P53011	WD _t	2.55444	6.04298	5.82521	6.03438	9.21490
P53196	WD _t	2.57434	5.94245	5.94724	6.20144	6.54197
P54311	WD _t	2.77647	6.03088	5.85735	6.12500	9.96471
P55735	WD _t	2.75155	5.86180	5.79037	5.96739	9.56832
P61964	WD _t	3.37575	6.11826	5.95359	6.08832	9.97305
P61965	WD _t	3.37575	6.11826	5.95359	6.08832	9.97305
P62871	WD _t	2.77647	6.03088	5.85735	6.12500	9.96471
P62881	WD _t	2.69747	5.92911	5.86329	6.13165	9.76709
P63005	WD _t	3.07561	5.93293	5.89878	6.03293	9.96463
P63244	WD _t	2.84700	5.94322	5.83912	6.06625	9.91167
P78406	WD _t	2.50272	5.78668	5.71060	5.96603	9.93071
P78774	WD _t	2.69629	6.02653	5.93899	6.09019	7.20424
P78972	WD _t	2.80533	6.03381	5.89037	6.16906	7.39857
Q02793	WD _t	2.66877	5.98741	5.91688	6.15113	6.59950
Q03774	WD _t	2.73198	5.98311	5.94257	6.05743	7.34797
Q04491	WD _t	2.68013	5.89226	5.90236	6.06397	9.52862
Q04724	WD _t	2.96234	6.08117	5.96299	6.21623	9.80065
Q05583	WD _t	2.69697	6.08939	5.89848	6.18333	7.92121
Q09028	WD _t	2.80118	6.04471	5.98118	6.01647	9.89412
Q11176	WD _t	2.95172	5.98691	5.91326	6.09820	8.57201
Q13216	WD _t	2.69192	5.89268	5.90530	6.03409	9.45455
Q16576	WD _t	2.65059	6.02118	5.98824	5.99765	9.82588
Q24572	WD _t	2.70000	5.99651	5.96628	5.99884	9.45698
Q24D42	WD _t	2.53499	5.81924	5.79883	6.01458	8.55685
Q2YDS1	WD _t	2.79839	6.00504	5.90423	6.18044	7.13407
Q58CQ2	WD _t	2.57527	5.98790	5.91532	6.06855	9.56452
Q6CN23	WD _t	2.57965	5.80531	5.88201	5.96755	6.28614
Q8LNY6	WD _t	2.65526	5.90395	5.88553	6.00132	7.77500
Q921E6	WD _t	2.50227	5.92971	6.24490	6.08617	9.93991
Q92466	WD _t	2.57260	5.96487	5.90867	6.07728	8.86768
Q969H0	WD _t	3.17751	6.15842	6.00424	6.24470	9.45686
Q96MX6	WD _t	2.56162	6.00280	5.80392	6.02521	9.85154
Q9GZS3	WD _t	2.86721	5.94098	6.00328	6.17705	9.92951
Q9Y297	WD _t	2.90992	6.00000	5.92066	6.06446	9.96446

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